Remarks

Prior to this filing, claims 39-45 were pending in this application and allowed. Claims 39-45 are canceled herein and new claims 46-72 are added.

New claims 46-66 correspond to original claims 1, 6-11, 13-18, 21, 26-28, 32-34 and 38, respectively, and derive support from these original claims and the specification at page 7, lines 17-18 and at page 8, lines 5-6 (with respect to the humanized equivalent of the monoclonal antibody obtained from hybridoma 1D11.16). Support for new claims 67-72 can be found in the specification at least at page 7, lines 17-18 and at page 8, lines 5-14.

No new matter has been added by these amendments. After entry of this amendment, **claims 46-72 are pending**. Unless specifically stated otherwise, none of these amendments are intended to limit the scope of any claim; Applicants reserve the right to pursue any removed subject matter in a related application.

This filing is appropriate after a Notice of Allowance, and no petition is required to withdraw this application from issuance, as the issue fee has not been paid and the response accompanies an RCE under 37 C.F.R. §1.114 that is submitted before the November 27, 2008 deadline to respond to the Notice of Allowance. Thus, this application is withdrawn from allowance. Applicants respectfully request that the Examiner enter this Amendment.

Notice of Allowance

Applicants thank Examiner Huff for withdrawing the rejection of claims 39-45 under 35 U.S.C. §112, first paragraph.

Applicants' Arguments

This Amendment and Response addresses the remaining rejections in the Final Office action dated May 12, 2008. In the Final Office action, original claims 1, 6-11, 13-18, 21, 26-28, 32-34 and 38 were rejected under 35 U.S.C. §103. As new claims 46-66 correspond to original claims 1, 6-11, 13-18, 21, 26-28, and 32-34 and 38, respectively, the following discussion

addresses the remaining rejections as if they had been made against new claims 46-66. Original claims 39-45 were allowed in response to the Amendment and Response After Final Action submitted on August 12, 2008, but are canceled herein.

Claim Rejections Under 35 U.S.C. §103

Dasch *et al.* in view of Barbera-Guillem and Rosenblum

Applicants believe it likely the Office might reject new claims 46-50, 52-55, and 59-65 (corresponding to original claims 1, 6-9, 11, 13-15, 21, 26-28, and 32-34) under 35 U.S.C. §103 as obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of Barbera-Guillem (U.S. Patent No. 6,224,866) and Rosenblum (U.S. Patent Application No. 2005/0214307) because the combination of references allegedly teaches "that compounds that treat tumors can also be used to treat tumor recurrence" (Office action dated November 8, 2007, at page 5). Applicants strenuously traverse this rejection to the extent it might be applied to the pending claims.

The United States Patent and Trademark Office has provided Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* Based on those Guidelines, the Office must provide the appropriate rationale to support rejections under 35 U.S.C. §103. More specifically, the Guidelines provide the following non-exclusive rationales for supporting a finding that a claimed invention is obvious (with emphasis added):

(A) combining prior art elements according to known methods to yield **predictable** results;

(B) simple substitution of one known element for another to obtain **predictable** results;

(C) use of known technique to improve similar devices (methods, or products) in the same way;

(D) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "obvious to try" - choosing from a finite number of identified, **predictable** solutions, **with a reasonable expectation of success**;

(F) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been **predictable** to one of ordinary skill in the art; and

(G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The emphasis in the Guidelines is accordingly the **predictability** of the combination, as a basis for a finding that there is a reasonable expectation of success associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of prior art, and accordingly no reasonable expectation of success.

As admitted in the November 2007 Office action, Dasch *et al.* does not specifically discuss the treatment of tumor recurrence (nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence). The current Office action combines Dasch *et al.* with two other references (Barbera-Guillem and Rosenblum) which allegedly make up for the deficiency of Dasch *et al.* Applicants respectfully disagree.

In view of the current USPTO Guidelines regarding obviousness, Applicants submit that the claimed elements could not have been combined, even in view of Dasch *et al.*, Barbera-Guillem, and Rosenblum, to **predictably** yield the claimed invention. Barbera-Guillem and Rosenblum both disclose antibodies, but that is where the similarity with the claimed methods ends. For example, Barbera-Guillem discloses the use of an immunotherapeutic composition that binds directly to B cells (for example, anti-CD20, anti-Lym-1, or anti-CD19 antibodies) in order to cause B cell depletion and reduce a pro-tumor immune response (see for example, column 3, line 1 through column 4, line 14; column 5, lines 57-63). Barbera-Guillem does not teach the 1D11 antibody, nor does it teach an antibody that can bind soluble TGF-beta.

In contrast to the antibodies disclosed in Barbera-Guillem, the 1D11.16 antibody of the claimed methods does not bind B cells or deplete B cells; rather, it binds TGF-beta which is released from non-T-non-B cells (see, for example, the specification at page 31, lines 26-29). More specifically, the 1D11 antibody blocks an immunosuppressive effect of TGF-beta in order to increase immunosurveillance by B cells or T cells (see, for example, page 19, lines 23-32 and

Example 5). In other words, the 1D11.16 antibody acts to increase the biological activity of B cells and T cells, whereas the antibody disclosed in Barbera-Guillem effectively acts to decrease the biological activity of B cells by depleting them. Thus, as the antibodies disclosed in Barbera-Guillem function by a completely different mechanism than the 1D11.16 antibody, the Barbera-Guillem antibodies therefore provide no reliable guidance for the activities exhibited by the 1D11.16 antibody, nor are they at all **predictive** of Applicants' use of this antibody.

Rosenblum discloses that one specific agent used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The "agent" of Rosenblum is an immunoconjugate comprised of a monoclonal antibody or a single chain antibody linked to a cytotoxic moiety, where the antibody moiety recognizes the cell surface protein GP 240 and thereby targets the cytotoxic moiety to a tumor cell expressing this antigen (paragraph [0013]). The purpose of the antibody moiety aspect of that "agent" is to target the cytotoxin (the active component of the immunoconjugate) to the GP 240-expressing tumor cell (paragraph [0015]). Thus, the "antibody" disclosed in Rosenblum is not, *per se*, inhibiting the tumor recurrence; it is simply targeting the anti-tumor cytotoxin to the tumor cell. Like Barbera-Guillem, Rosenblum does not disclose the 1D11.16 antibody or another antibody that inhibits TGF-beta activity. Thus, nothing about the Rosenblum agent would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11.16 antibody, nor is it **predictive** in any way of Applicants' use of this antibody.

Antibodies, like drugs, are a generic class of compounds. Just as one would not conclude that two completely different drugs, having different mechanisms of action, could be used to treat the same disease, one should not extrapolate that two different antibodies that function by wholly different mechanisms would have **predictably** the same biological effect. The mere fact that Rosenblum and Barbera-Guillem disclose antibodies or antibody fusion proteins that are used in some way to inhibit tumor recurrence is not, on its own, **predictive** of the claimed method, which uses a completely different antibody having a completely different mechanism of action than the antibodies disclosed in these references (see Amendment and Response submitted on April 8, 2008, for details related to the mechanism of action of the 1D11.16 antibody). Neither Barbera-Guillem nor Rosenblum disclose an antibody that binds TGF-beta or that blocks

an immunosuppressive effect of TGF-beta, as required by the claims, which are specifically directed to the use of the 1D11.16 antibody. As antibodies belong to the "unpredictable" art of biotechnology, and because the antibodies disclosed in Barbera-Guillem and Rosenblum function by different mechanisms than the 1D11 antibody, one of skill in the art **would not have predicted** that the combination of elements in these references and in Dasch *et al.* would yield the claimed invention.

Applicants respectfully submit that the disclosures of Barbera-Guillem and Rosenblum are not predictive that an antibody which blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor and these references cannot be combined with Dasch *et al.* Accordingly, Applicants submit that new claims 46-50, 52-55, and 59-65 are not obvious in view of the rationales defined under the Guidelines set forth above, and request that this rejection be withdrawn.

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Suthanthiran *et al.*

Applicants believe it likely the Office might reject new claims 46-55 and 59-66 (corresponding to original claims 1, 6-11, 13-15, 21, 26-28, 32-34 and 38) under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333). Applicants respectfully traverse this rejection to the extent it might be applied to the pending claims.

The Office action states that Suthanthiran *et al.* discloses the use of TGF-beta antagonists, including monoclonal antibodies, "to *treat* a variety of different cancers known to be associated with TGF-beta" (Office action at page 7, emphasis added). However, Suthanthiran *et al.* **does not** teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. Nor does Suthanthiran *et al.* disclose the concept of tumor recurrence. Thus, Suthanthiran *et al.* does not make up for the deficiencies of Dasch *et al.*

As discussed above, the disclosures of Barbera-Guillem and Rosenblum are not predictive that an antibody that blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor, and Dasch *et al.* and Suthanthiran *et al.* do not implicitly or explicitly

teach all elements of the claimed methods. Thus, Applicants' claims are non-obvious over the combination of cited references. Withdrawal of this rejection is requested.

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Terabe *et al.*

Applicants believe it likely that the Office might reject new claims 46-50 and 52-66 (corresponding to original claims 1, 6-9, 11, 13-18, 21, 26-28, 32-34 and 38) under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000). Applicants respectfully traverse this rejection to the extent it might be applied to the pending claims.

The Office action states that Terabe *et al.* shows that the "assays of claims 16-18 are known in the art . . . and are used in tumor immunosurveillance" (Office action at page 8). However, Terabe *et al.* **does not** teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. As discussed above, Dasch *et al.* does not teach methods of inhibiting tumor recurrence. Thus, Terabe *et al.* does not make up for the deficiencies of Dasch *et al.* In addition, as discussed above, the disclosures of Barbera-Guillem and Rosenblum are not predictive that an antibody that blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor and these references cannot be combined with Dasch *et al.* Thus, Applicants' claims are non-obvious over the cited references. Withdrawal of this rejection is requested.

Request for Examiner Interview

Applicants believe the application is in condition for allowance and such action is requested. If the present rejections are maintained, or an additional rejection is asserted, Examiner Huff is formally requested to contact the undersigned in order to arrange a telephonic interview prior to issuance of the next Office action. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview can be arranged in advance by a written request.

Respectfully submitted,

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